



# **Armed Forces College of Medicine AFCM**





# **1- Gluconeogenesis**

## **BY**

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# INTENDED LEARNING OBJECTIVES (ILOs)



**By the end of this lecture the student will be able to:**

1. Discuss Biochemical importance of gluconeogenesis
2. Mention different gluconeogenic substrates
3. Illustrate different gluconeogenesis pathways



# Outlines

**What is gluconeogenesis**

**Gluconeogenic substrates**

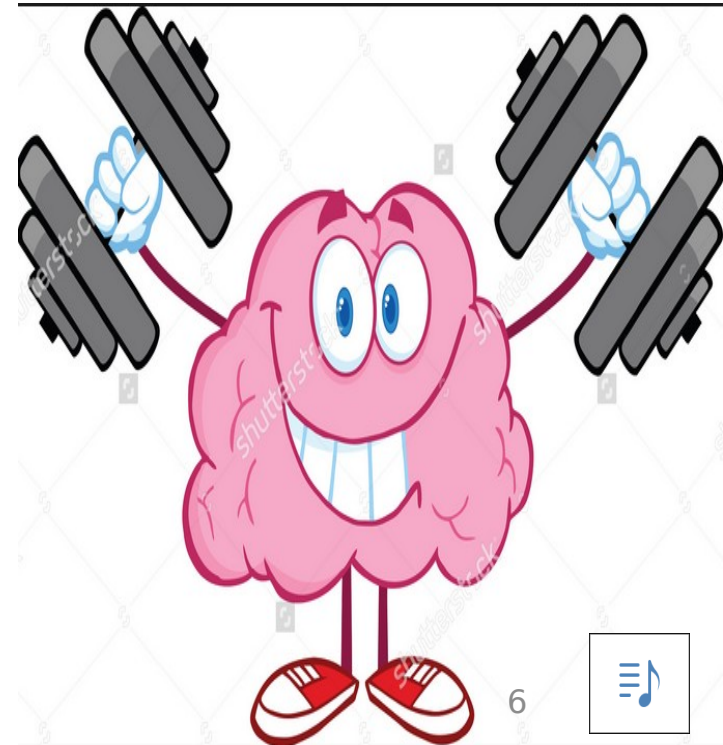
**Gluconeogenesis pathways**

**Biochemical importance of gluconeogenesis**

# **What is gluconeogenesis**

# Brain fuels

- They are food stuffs that supply the brain with energy.
- The brain is an **energy-hungry organ** as it uses **ten times** more energy than the rest of the organs.



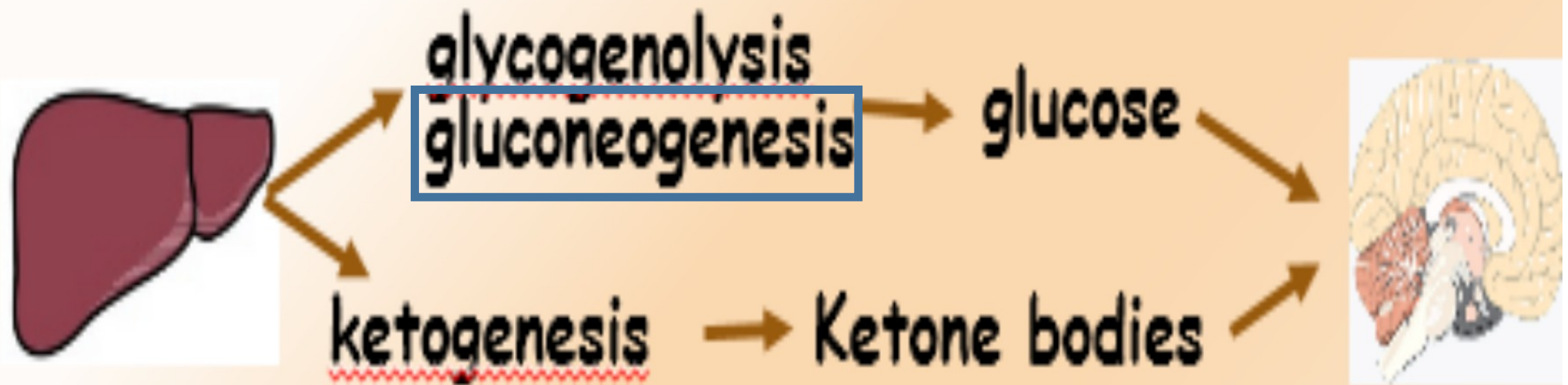
**What are the different sources of brain fuels during **well-fed state**?**



**Dietary carbohydrates** are digested giving **glucose** which is the main fuel of the brain.



# What are the different sources of brain fuels during **fasting state**?



# Case presentation

**A patient 45 years old  
with a history of liver cell  
failure developed  
hypoglycemia during  
prolonged fasting**

**WHY?**





**After an overnight fast, 75-80% of glucose released into the circulation derives from the liver and the remaining 20-25% derives from the kidneys**





# Gluconeogenesis

**All pathways responsible for formation of glucose from non carbohydrate sources.**

***Examples:* lactate ,aminoacids, glycerol & propionyl CoA**



# Organs involved in gluconeogenesis

- In **liver** (major site) & **kidney cortex**. These organs contain **complete set of enzymes** required for synthesis of glucose from non carbohydrate sources
- Occurs **partially** in **mitochondria** and **partially** in the **cytosol**



# **Gluconeogenic substrates**

# Substrates of

**Lactate**

**Glycero  
l**

**Amino  
acids**

**Propiony  
l COA**



# **Gluconeogenesis pathways**

# 1- Gluconeogenesis from lactate

## Sources of Lactate:

From **anaerobic** tissues as:

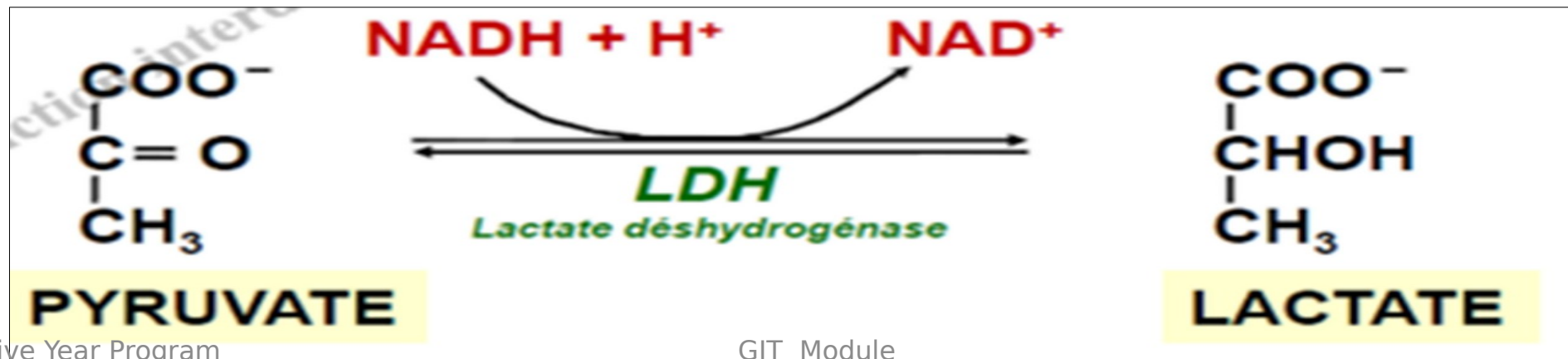
RBCs,  
Renal medulla,  
Retina,  
Lens,  
Testis, **and**

From severe muscular exercise



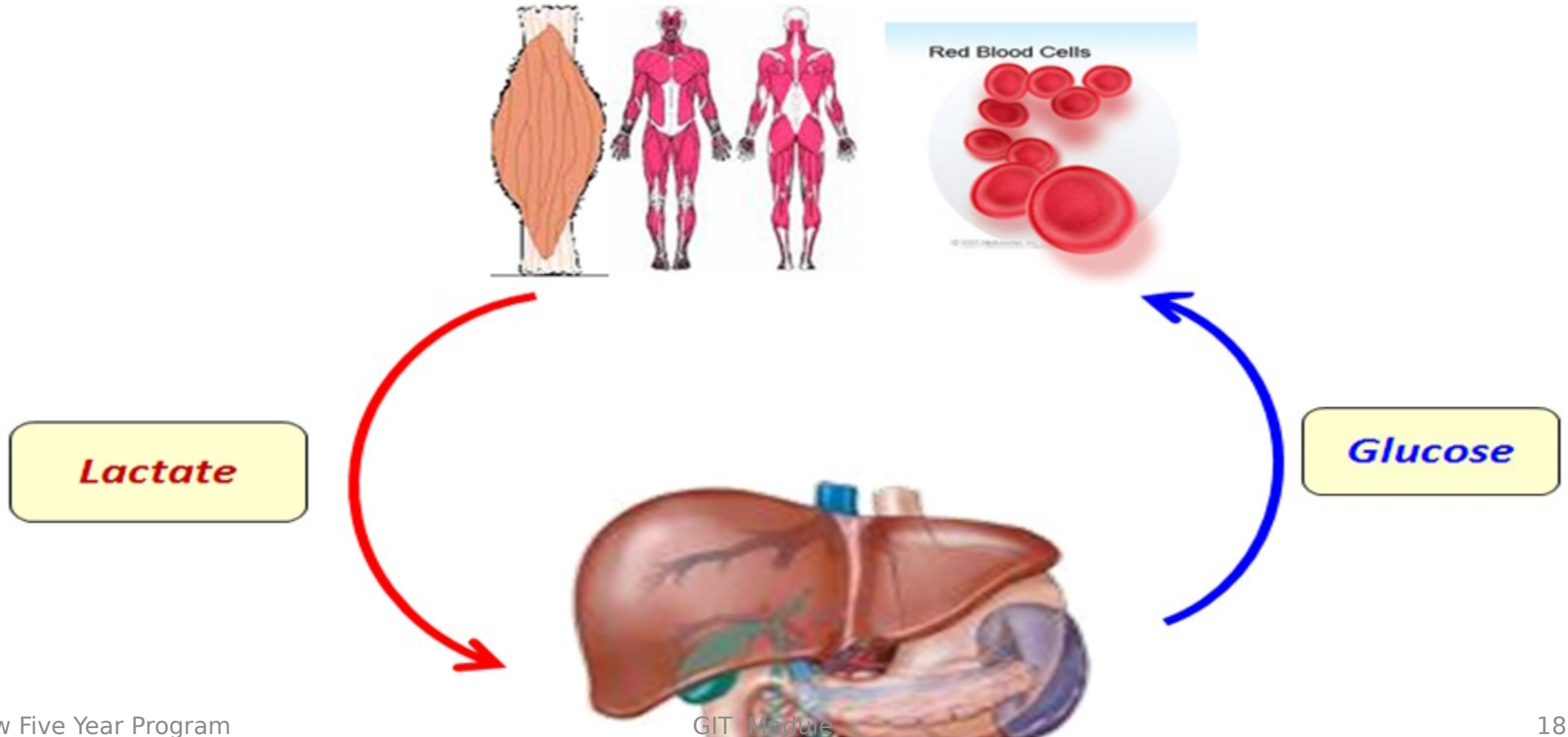
# 1- Gluconeogenesis from lactate

Lactate is released & delivered to the **liver** and **reconverted** to pyruvate by **lactate dehydrogenase** then →→ glucose (by gluconeogenesis), which is released back into the



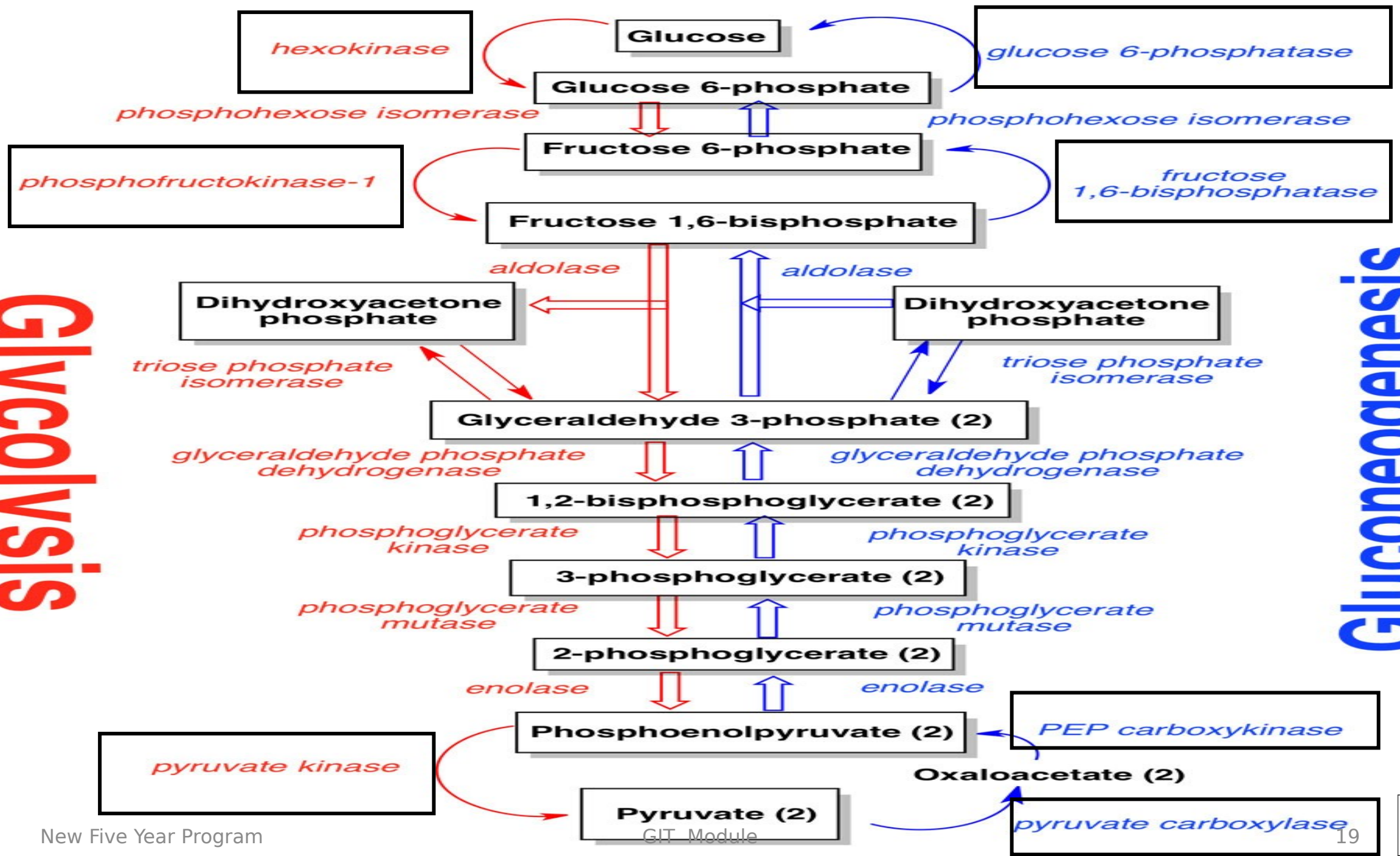
# 1- Gluconeogenesis from

## Cori Cycle



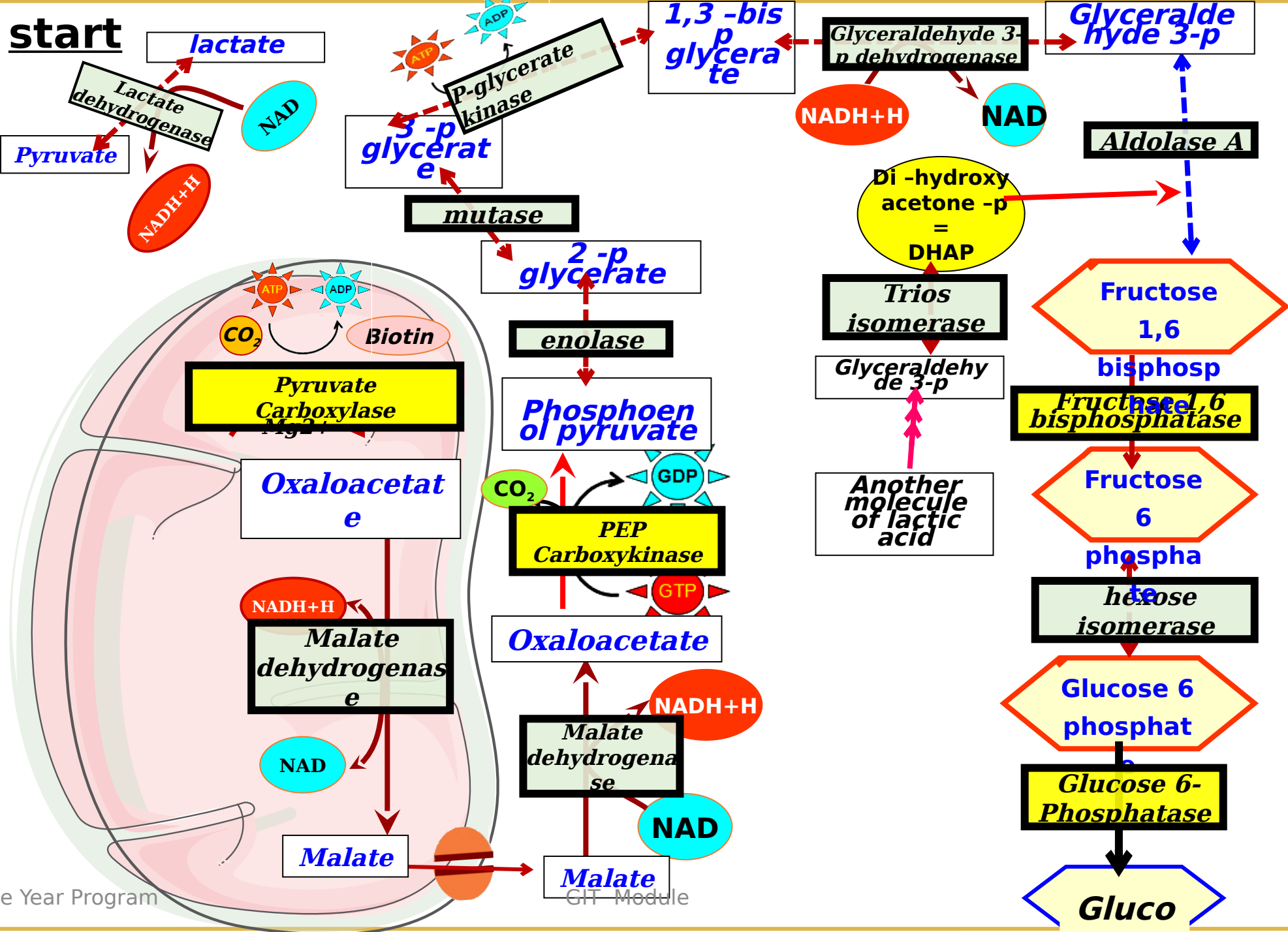


# Glycolysis



# Gluconeogenesis







## Note:

- we need **2 lactate** molecules to produce **one glucose** molecule
- Pyruvate carboxylase enzyme is a **mitochondrial** enzyme
- **PEPCK** reaction is driven by hydrolysis of **GTP**.



# The 3 irreversible enzymes of glycolysis are reversed as follow:

- **Pyruvate Kinase:** by Pyruvate Carboxylase & phosphoenol pyruvate carboxykinase (PEPCK).
- **PhosphoFructoKinase I:** by Fructose 1,6 bisphosphatase.
- **Hexokinase/glucokinase:** by Glucose 6 phosphatase.



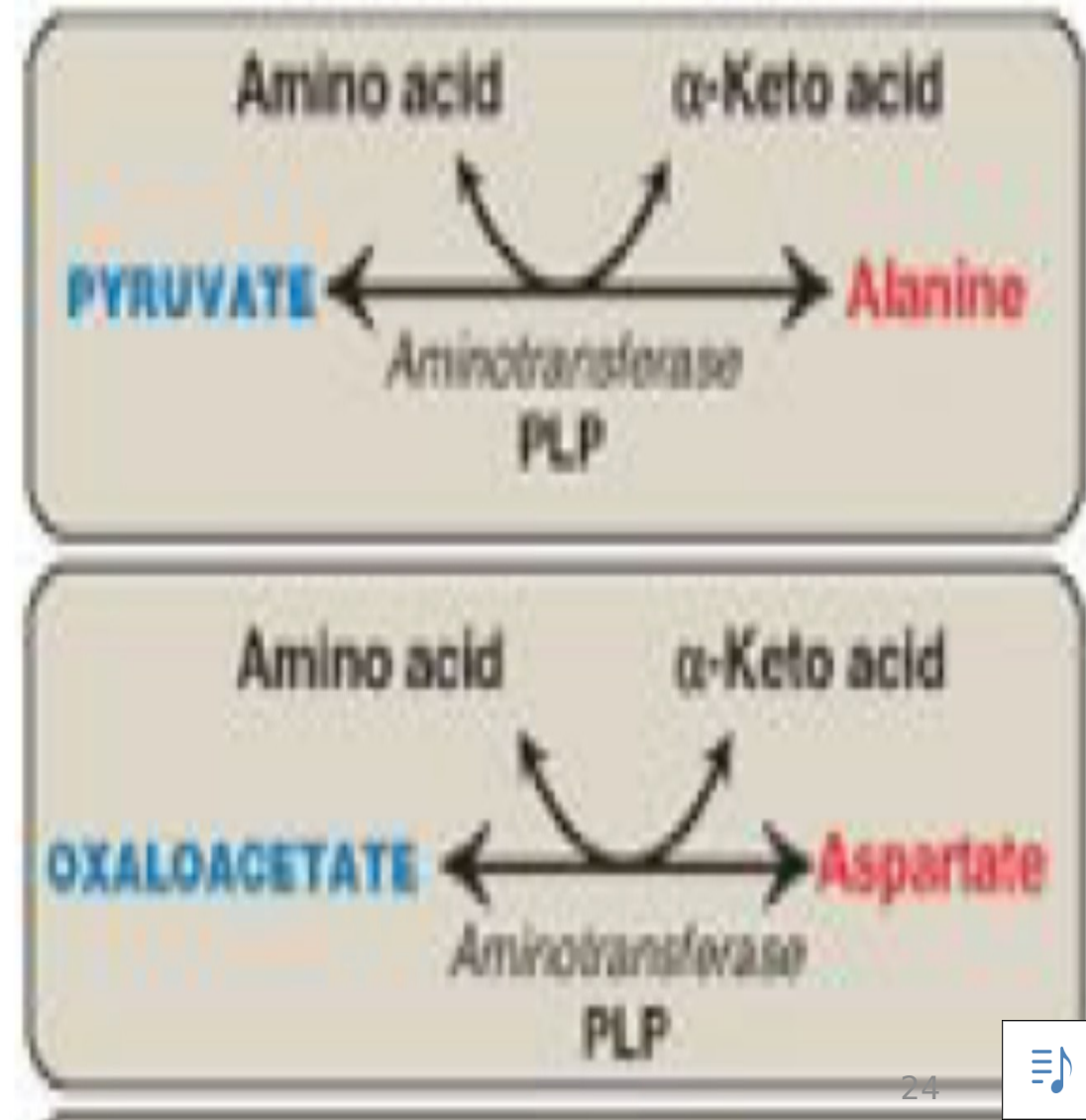
## 2- Gluconeogenesis from Amino acids

- Aminoacids (mostly **Alanine & glutamine**) from muscle proteolysis are the **major source** of glucose during **prolonged** fasting & starvation.



# 2- Gluconeogenesis from Amino acid

- Amino acids are metabolized 1st to **release NH<sub>3</sub>** through **deamination** or **transamination** to give **pyruvic** or **oxalacetate**



## 2- Gluconeogenesis from Amino acids

**Alanine** is one of the **predominant** aminoacid released during prolonged fasting from **muscle** & delivered to the liver

and **reconverted** to glucose by **Alanine transaminase**, which is

released back into the circulation

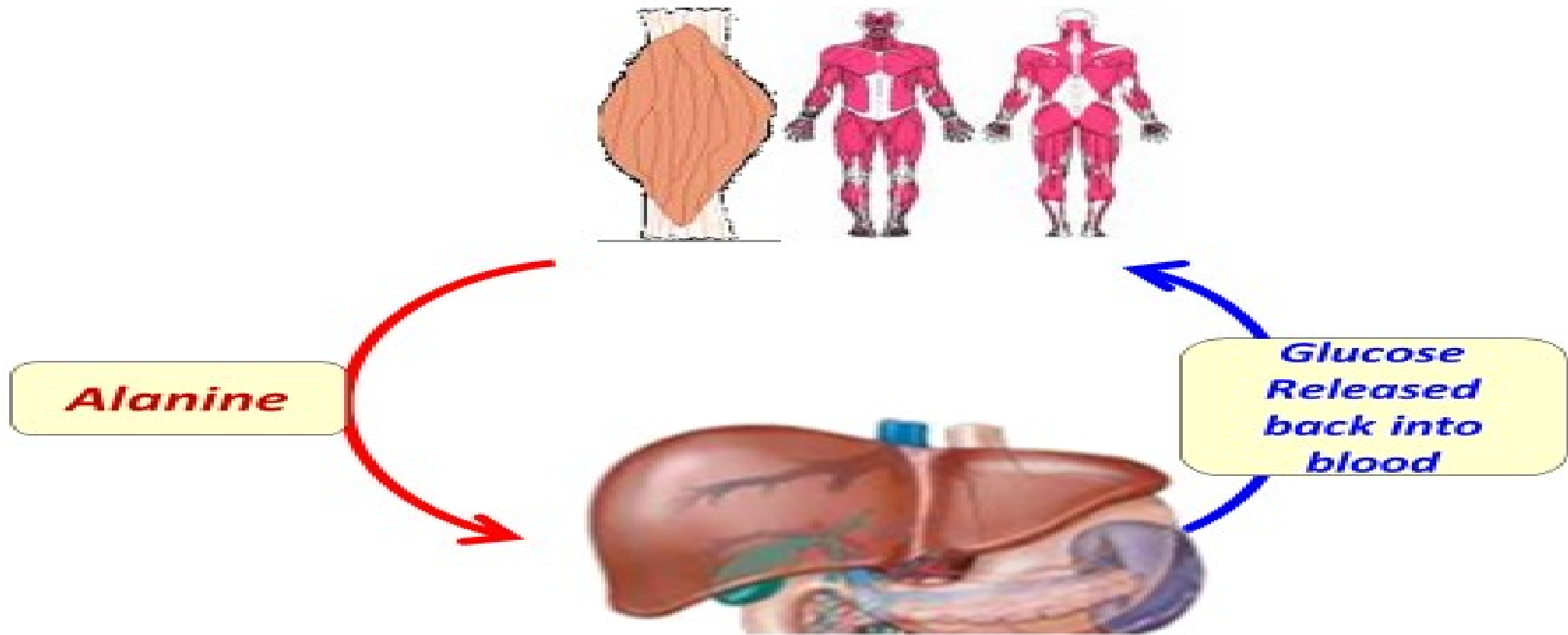
(**Glucose-alanine Cycle**).





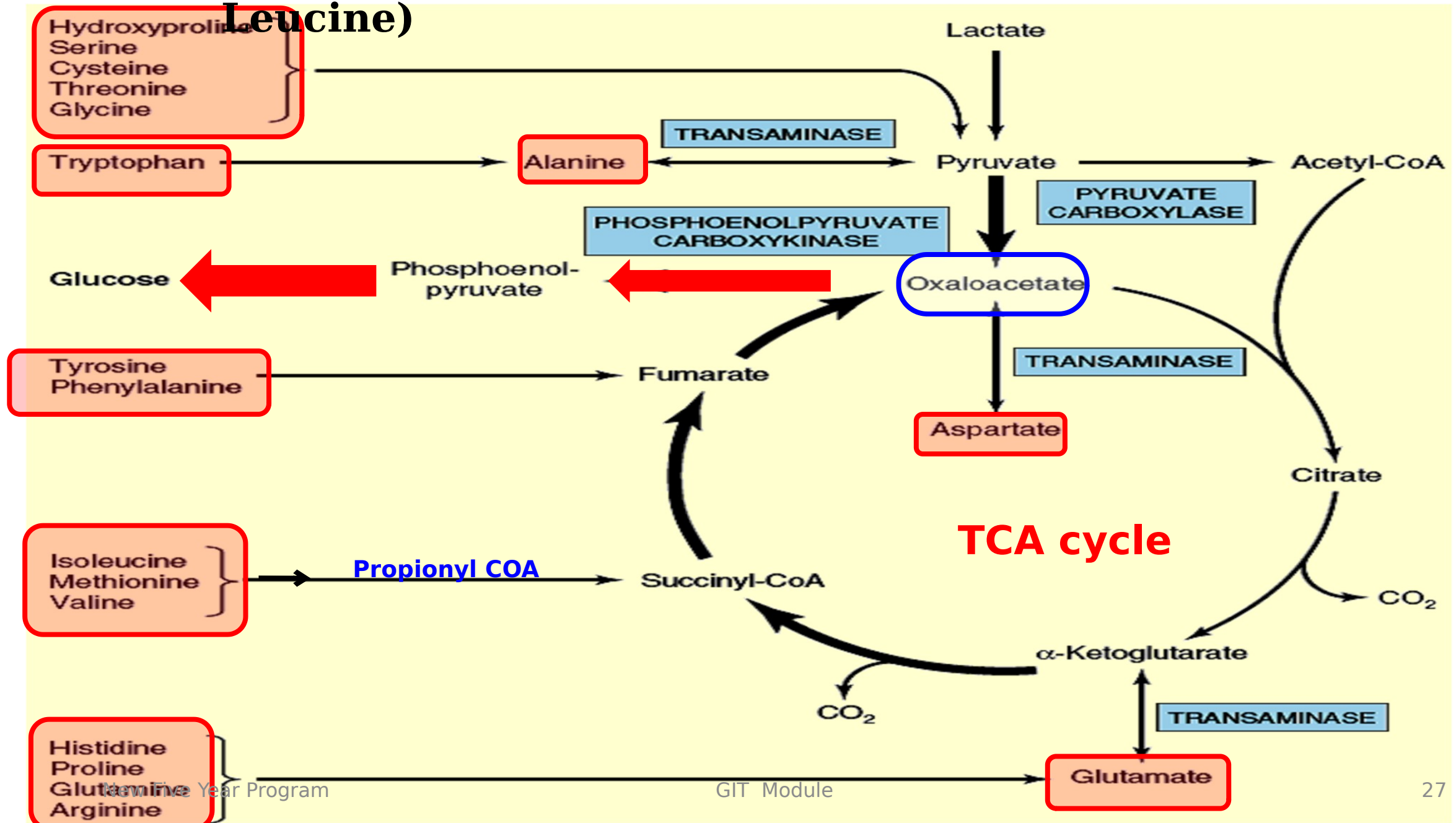
# 2- Gluconeogenesis from Amino acids

## Glucose-alanine Cycle



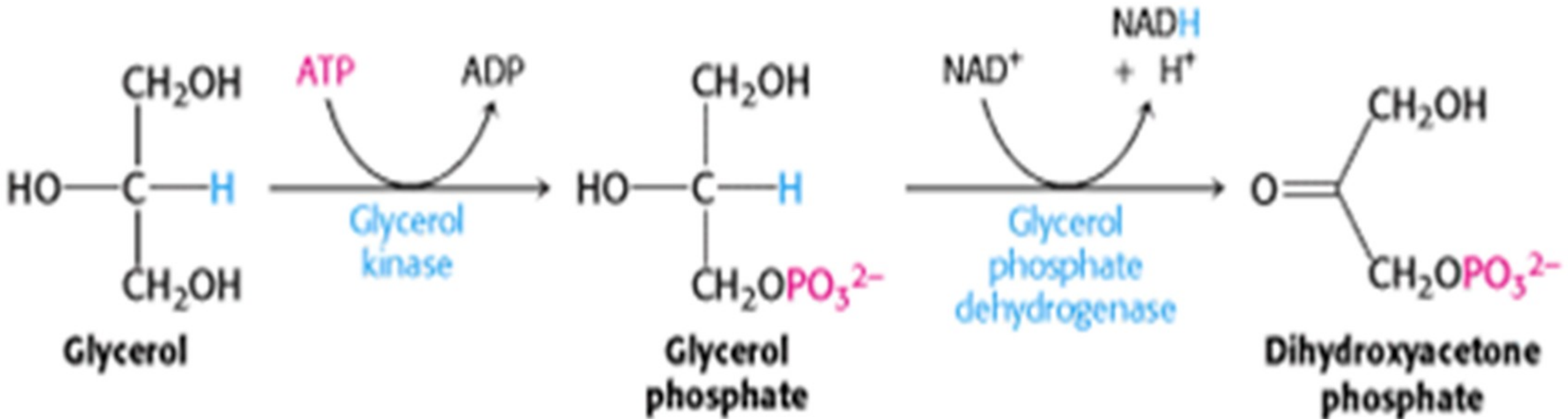


# All A.As can give →→ Glucose Except (Lysine & Leucine)



# 3- Gluconeogenesis from Glycerol

- Glycerol is released during **Lipolysis** & delivered to the liver.



# 4- Gluconeogenesis from Propionyl CoA

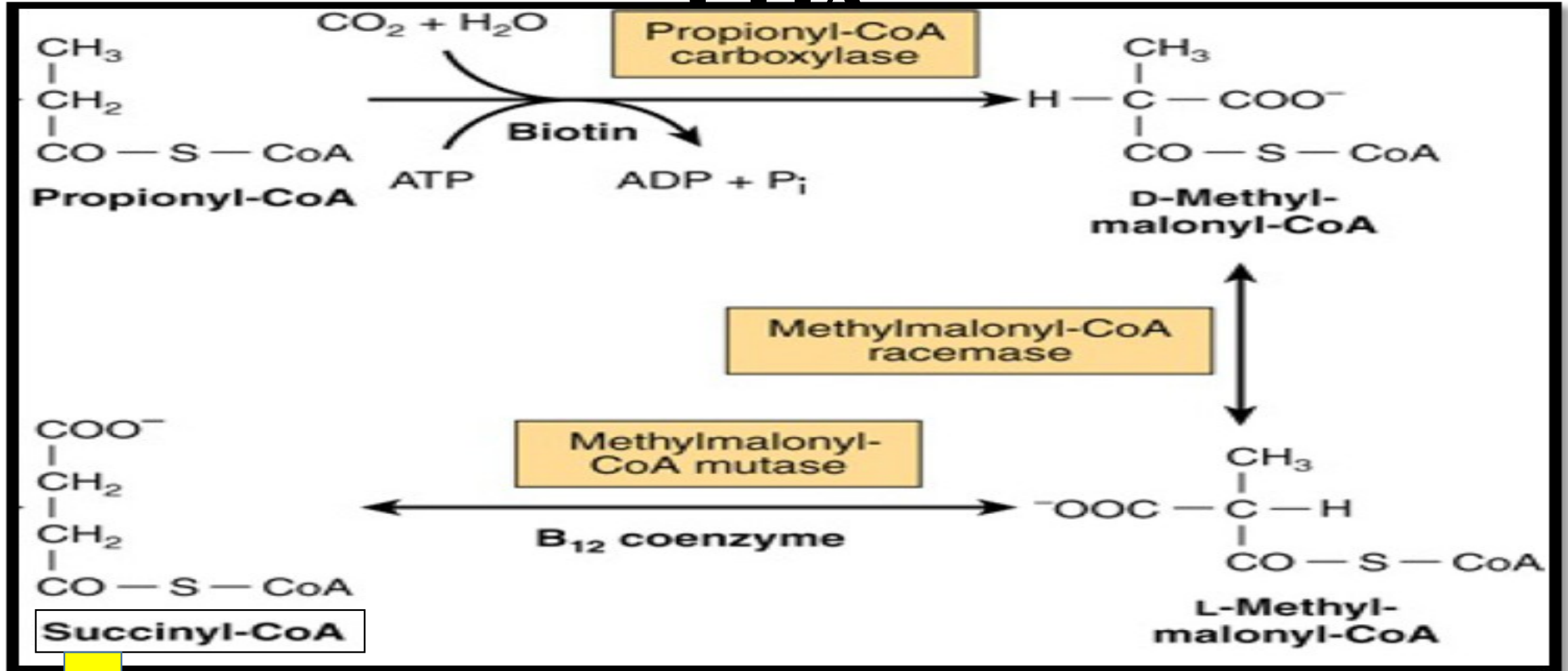
It is a product of **oxidation of odd-number fatty acids** & catabolism of amino acids as **valine , isoleucine & methionine**.

***N.B.***

***It is not a significant glucogenic precursor in human beings***



# 4- Gluconeogenesis from Propionyl CoA



↓  
**Glucose**



## Lecture Quiz



**Which one of the following reactions is unique to gluconeogenesis?**

- A. Lactate  $\rightarrow$  pyruvate**
- B. Phosphoenolpyruvate  $\rightarrow$  pyruvate**
- C. Oxaloacetate  $\rightarrow$  phosphoenolpyruvate**
- D. Glucose 6-phosphate  $\rightarrow$  fructose 6 phosphate**
- E. 1,3-Bis-phosphoglycerate  $\rightarrow$  3-phosphoglycerate**



# Energy requirement in gluconeogenesis to form 1 glucose molecule is dependant on starting point:

- Starting with 2 **pyruvate** cost **6** ATP:  $2 \times (1 \text{ ATP for pyruvate carboxylase} + 1 \text{ ATP for phosphoglycerate kinase} + 1 \text{ GTP for PEPCK})$
- Starting with 2 **oxaloacetate** cost **4** ATP
- Starting with 2 **glycerol** we need **2** ATP

***Gluconeogenesis is a costly metabolic process***



# **Biochemical importance of gluconeogenesis**

# Biochemical importance of gluconeogenesis

1. Maintain a **basal level of glucose** in the circulation during **prolonged fasting & starvation** this is because...

- *Brain has a minimum requirement of **120g** glucose/day*
- *Glucose is the main source of energy to anaerobic cells ex: RBCs*

2. Gluconeogenesis also help To **clear lactate** and prevent lactic acidosis.





# **So, gluconeogenesis is active in the following conditions:**

**1- During prolonged fasting & starvation:** it begins nearly 6 hrs after last meal & become **fully active after complete depletion** of liver glycogen (10-18 hrs).

**2- Unbalanced diet** (decrease carbohydrates & increase fat and/or protein).



**So, gluconeogenesis is active in the following conditions:**

**3- Type I diabetes mellitus** (stimulation of enzymes of gluconeogenesis).

**4- Cushing syndrome** (high cortisol level stimulate muscle proteolysis & enzymes of gluconeogenesis).

**5- Severe muscle exercise** (increase lactate which is a substrate of gluconeogenesis).



# Take Home Message

- **Gluconeogenesis:**  
**Synthesis of glucose from noncarbohydrates**  
**Anabolic & Energy-consuming**
- **Four unique enzymes are required for the reversal of the 3 irreversible reactions of glycolysis**
- **Both gluconeogenesis & glycolysis are reciprocally-regulated**
- **Impaired gluconeogenesis leads to fasting hypoglycemia and may cause lactic acidosis**



Thank  
you

